REMARKS

By the present amendment, Claims 8, 11, 17, 19-20, 22-23, 25, 28-49, and 52 have been cancelled without prejudice or disclaimer. Claims 1-2, 9, 12-16, 18, 21, 24, 26-27, and 50 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications. Claims 3-7, 10, and 51 are currently being examined on the merits.

Comments regarding restriction requirement

Claims 9, 12-14, and 26-27 are "method of making" and "method of use" claims which all ultimately depend from polynucleotide product Claims 4 and 10. Therefore, upon allowance of Claims 4 and 10, it is believed that Claims 9, 12-14, and 26-27 should be rejoined and considered, in accordance with the commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103 (b)."

Utility rejection under 35 U.S.C. §§ 101 and 112, first paragraph

The Examiner has rejected claims 3-7, 10-11, and 51-52 under 35 U.S.C. § 101, because the claimed invention is not supported by either a specific asserted utility or a well-established utility. The rejection alleges in particular that:

- "...none of the recited utilities in the specification are specific to the SEQ ID NO:26". (Office Action, January 12, 2004, page 3).
- "Further experimentation would be required of the skilled artisan to reasonably confirm a real world use for the claimed polynucleotide and polypeptide it encodes". (Office Action, January 12, 2004, page 5).

The rejection of claims 3-7, 10-11, and 51-52 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue is a polynucleotide corresponding to a full-length expressed genetic markers that is expressed in reproductive, gastrointestinal, and nervous tissues in humans. The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions.

Applicants submit three expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references filed before or shortly after the May 14, 1999, priority date of the instant application. The Rockett Declaration, Iyer Declaration, Bedilion Declaration, and the ten (10) references establish that, prior to the May 14, 1999 filing date of the parent application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;
>
> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;
>
> nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function, or the biological function of the polypeptide it encodes. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the the Rockett Declaration, the Iyer Declaration, and the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise biological function.

Enablement rejection under 35 U.S.C. § 112, first paragraph

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility (Office Action, January 12, 2004, page 5). To the extent that the rejection under § 112, first paragraph, is based on improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

In addition, Claims 3-7, 10-11, and 51-52 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed polynucleotide fragments. In particular, the Office Action asserts that "the ordinary artisan would be required to perform undue experimentation to identify any polypeptide, which was an active fragment of the polynucleotide of the presently claimed invention". (Office Action, January 12, 2004, page 6).

The claims have been amended to delete the "fragment" language. In addition, Claims 11 and 52 have been cancelled. By these amendments, Applicants expressly do not disclaim equivalents of the claimed invention. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

For at least the above reasons, withdrawal of the enablement rejection is requested.

Written description rejection under 35 U.S.C. §§ 112, first paragraph

Claims 3-7, 10-11, and 51-52 have been rejected under the first paragraph of 35 U.S.C. § 112, first paragraph, for alleged lack of an adequate written description. According to the Office Action, "[t]he claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Office Action, January 12, 2004, page 6). In particular, the Office Action asserts that there is not an adequate written description of the recited polynucleotide "fragments" and "variants". This rejection is respectfully traversed.

The claims have been amended by deleting the "fragment" language. Claims 11 and 52 have been cancelled. By these amendments, Applicants expressly do not disclaim equivalents of the claimed invention. Applicants do not concede to the Patent Office position; Applicants are amending the claim solely to obtain expeditious allowance of the instant application.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Attention is drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the recited "variants" of SEQ ID NO:6

The subject matter encompassed by claims 3-7, 10, and 51 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent Claim 3 recites a polynucleotide encoding "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:6", and the "variant" language of independent claim 10 recites "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:26."

The amino acid sequence of SEQ ID NO:6 and the polynucleotide sequence of SEQ ID NO:26 are explicitly disclosed in the specification. See, for example, the Sequence Listing. Variants of SEQ ID NO:6 and SEQ ID NO:26 are described in the Specification at, for example, page 11, line-34 to page 12, line 18.

One of ordinary skill in the art would recognize polynucleotide sequences which are variants having a polynucleotide sequence at least 90% identical to SEQ ID NO:26, or which encode polypeptide variants having an amino acid sequence at least 90% identical to SEQ ID NO:6. Given any naturally occurring polynucleotide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:26, or whether it encoded a variant of SEQ ID NO:6. Accordingly, the specification provides an adequate written description of the recited polynucleotide variants of SEQ ID NO:26 and polynucleotides encoding polypeptide variants of SEQ ID NO:6.

There simply is no requirement that the claims recite particular amino acid "variant" sequences because, as discussed above, the Specification already provides sufficient structural definition of the claimed subject matter. Because the recited amino acid "variants" are defined in terms of SEQ ID NO:6, the precise chemical structure of every amino acid variant within the scope of the claims can be discerned. Accordingly, the Specification provides an adequate written description of the claimed sequences. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention.

1. The present claim specifically defines the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to

consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35

U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides which code polypeptides in terms of chemical structure, rather than functional characteristics. For example, the "variant" language of independent Claim 3 and Claim 10 recites chemical structure to define the claimed genus:

Claim 3:

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:6, and

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:6.

Claim 10:

10. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:26,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:26,

c) a polynucleotide fully complementary to a polynucleotide of a),

d) a polynucleotide fully complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:6 and SEQ ID NO:26. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides which are encoded by the polynucleotides. The polynucleotides and polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the

present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

Further, on page 9 of the Office Action, the Examiner has inappropriately relied upon the decision in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991) to assert inadequate written description in the subject application.

The independent claim at issue in *Amgen* reads as follows:

> 7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

As stated by the court at page 1026 in *Amgen*:

> Claim 7 is a generic claim, **covering all possible DNA sequences that will encode any polypeptide** having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of red blood cells. (emphasis added)

In addition, from the discussion at pages 1026-1027 it is apparent that the patentee of claim 7 in *Amgen* had engaged in making man-made analogs of erythropoietin. Thus, the subject matter defined by claim 7 in the *Amgen* case had no limitation as to whether the DNA sequences of the erythropoietin molecules were naturally-occurring or man-made. This is a situation far removed from the subject matter defined by the claims on appeal here, where the claims recite polypeptides comprising "a **naturally occuring amino acid sequence** at least 90% identical to the amino acid sequence of SEQ ID NO:6." As discussed at above, the present Specification describes how to make the claimed variants of SEQ ID NO:2 which comprise naturally-occurring sequences.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. (Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides which encode polypeptides related to the amino acid sequence of SEQ ID NO:6. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as full-length expressed genetic markers and which have as little as 30% identity over at least 150 residues to SEQ ID NO:6. The "variant language"of the present claims recites, for example, a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:6." This variation is far less than that of all potential full-length expressed genetic markers related to SEQ ID NO:6, i.e., those full-length expressed genetic markers having as little as 30% identity over at least 150 residues to SEQ ID NO:6.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of May 14, 1999. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:6 and SEQ ID NO:26, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly*, *Fiers,* and *Amgen*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly*, *Fiers,* and *Amgen*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:6 and SEQ ID NO:26. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides which encode the polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, withdrawal of this rejection is requested.

Indefinitness rejection under 35 U.S.C. § 112, second paragraph:

Claims 3-7, 10-11, and 51-52 were rejected under the second paragraph of 35 U.S.C. § 112 for alleged indefiniteness. This rejection is traversed.

The Office Action asserted that language relating to polynucleotides encoding various fragments of SEQ ID NO:6 polypeptide was unclear. To expediate prosecution of the subject

application, the "fragment" language has been deleted from the claims. Applicants expressly do not disclaim equivalents of the claimed subject matter.

In addition, Claim 3 has been placed in independent form, as requested by the Examiner.

For at least the above reasons, withdrawal of this rejection is requested.

Rejection under 35 U.S.C. § 102(b):

Claims 3, 6-7, and 10-11 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ansari-Lari et al. (Genome Res., Vol. 7(3), pages 268-280, 1997). In particular, the Office Action states that "Ansari-Lari et al. teach an isolated polynucleotide comprising a biologically active or immunogenic fragment of SEQ ID NO:26..." (Office Action, January 12, 2004, page 11).

To expedite prosecution of the subject application, the "fragment" language has been deleted from the claims, including cancellation of Claim 11. Applicants expressly do not disclaim equivalents of the claimed subject matter. Withdrawal of this rejection is threfore requested.

Rejections under 35 U.S.C. § 103(a):

Claim 52 has been rejected under 35 U.S.C. § 103(a) as obvious over Ansari-Lari et al. in view of Brennan (USPN. 5,474,796).

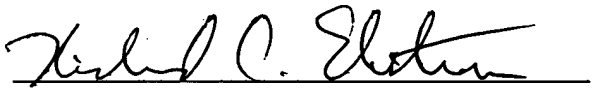
To expedite prosecution of the subject application, Claim 52 has been cancelled. Applicants expressly do not disclaim equivalents of the claimed subject matter. Withdrawal of this rejection is therefore requested.

CONCLUSION

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE CORPORATION

Date: March 30, 2004



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